

In the specification:

On page 1, starting on line 27 and ending on line 34, please replace the paragraph with the following amended paragraph:

This application is a continuation of and claims priority under 35 U.S.C. § 120 to co-pending application number 09/874,514, filed June 5, 2001, which application is a continuation application of and claims priority under 35 U.S.C. § 120 to 08/986,025, filed December 3, 1997, now U.S. Patent No. 6,242,469, issued June 5, 2001, which claims priority under 35 U.S.C. § 119(e) to U.S. Provisional Application Serial Nos. 60/032,282, 60/033,767, 60/047,941, and 60/055,533, filed December 3, 1996, January 14, 1997, May 22, 1997, May 29, 1997, and August 13, 1997, respectively, the contents of which are hereby incorporated by reference into this application. This invention was made with government support under grants CA-28824, CA-39821, CA-GM 72231, CA-62948, and AI0-9355 from the National Institutes of Health, and grant CHE-9504805 from the National Science Foundation. Additionally, the present invention was supported in part by a fellowship from the United States Army to Dongfang Meng (DAMD 17-97-1-7146), and thus the government has certain rights in the invention.

On page 3, lines 21-22, please replace the paragraph with the following amended paragraph:

Figures 3(A) and 3(B) provide syntheses of key iodinated intermediates used to prepare hydroxymethylene- and hydroxypropylene-substituted epothilone derivatives.

On page 3, lines 24-27, please replace the paragraph with the following amended paragraph:

Figures 3(C) and 3(D) provide methods of preparing hydroxymethylene- and hydroxypropylene-substituted epothilone derivatives, said methods being useful generally to prepare 12,13-*E* epothilones wherein R is methyl, ethyl, n-propyl, and n-hexyl from the corresponding *E*-vinyl iodides.

On page 3, lines 29-30, please replace the paragraph with the following amended paragraph:

Figures 3(E) and 3(F) show reactions leading to benzoylated hydroxymethyl-substituted desoxyepothilone and hydroxymethylene-substituted epothilone (epoxide).

On page 4, line 9, please replace the paragraph with the following amended paragraph:

Figures 6(A) and 6(B) provide a scheme of an olefin metathesis route to epothilone A and other analogues.

On page 4, line 29, please replace the paragraph with the following amended paragraph:

Figures 14(A) and 14(B) show the preparation of intermediate 4A.

On page 5, lines 7-8, please replace the paragraph with the following amended paragraph:

Figures 18(A) and 18(B) provide a synthetic pathway to a protected intermediate for 8-desmethyl deoxyepothilone A.

On page 5, lines 10-11, please replace the paragraph with the following amended paragraph:

Figures 19(A), 19(B) and 19(C) provide a synthetic pathway to 8-desmethyl deoxyepothilone A, and structures of *trans*-8-desmethyl-desoxyepothilone A and a *trans*-iodoolefin intermediate thereto.

On page 5, lines 13-22, please replace the paragraph with the following amended paragraph:

Figure 20(A) shows structures of epothilones A and B and 8-desmethylepothilone and Figure 20(B) shows a synthetic pathway to intermediate TBS ester 10 used in the preparation of desmethylepothilone A. (a) (*Z*)-Crotyl-B[(-)-Ipc]₂, -78°C, Et₂O, then 3N NaOH, 30% H₂O₂; (b) TBSOTf, 2,6-lutidine, CH₂Cl₂ (74% for two steps, 87% ee); (c) O₃, CH₂Cl₂/MeOH, -78°C, then DMS, (82%); (d) *t*-butyl isobutyrylacetate, NaH, BuLi, 0°C, then 6 (60%, 10:1); (e)

Me₄NBH(OAc)₃, -10°C (50%, 10:1 α/β) or NaBH₄, MeOH, THF, 0°C, (88%, 1:1 α/β); (f) TBSOTf, 2,6-lutidine, -40°C, (88%); (g) Dess-Martin periodinane, (90%); (h) Pd(OH)₂, H₂, EtOH (96%); (i) DMSO, oxalyl chloride, CH₂Cl₂, -78°C (78%); (j) Methyl triphenylphosphonium bromide, NaHMDS, THF, 0°C (85%); (k) TBSOTf, 2,6-lutidine, CH₂Cl₂, rt (87%).

On page 5, line 29, please replace the paragraph with the following amended paragraph:

Figures 22(A), 22(B) and 22(C) show a synthetic pathway to prepare epothilone analogue 27D.

On page 5, line 31, please replace the paragraph with the following amended paragraph:

Figures 23(A), 23(B) and 23(C) show a synthetic pathway to prepare epothilone analogue 24D.

On page 5, line 33, please replace the paragraph with the following amended paragraph:

Figures 24(A) and 24(B) show a synthetic pathway to prepare epothilone analogue 19D.

On page 5, line 35, please replace the paragraph with the following amended paragraph:

Figures 25(A), 25(B), 25(C) and 25(D) show a synthetic pathway to prepare epothilone analogue 20D.

On page 5, line 37, please replace the paragraph with the following amended paragraph:

Figures 26(A), 26(B), 26(C) and 26(D) show a synthetic pathway to prepare epothilone analogue 22D.

On page 6, lines 1-2, please replace the paragraph with the following amended paragraph:

Figures 27(A), 27(B) and 27(C) show a synthetic pathway to prepare epothilone analogue 12-hydroxy ethyl-epothilone.

On page 6, lines 4-7, please replace the paragraph with the following amended paragraph:

Figures 28(A) and 28(B) show the activity of epothilone analogues in a sedimentation test in comparison with DMSO, epothilone A and/or B. Structures 17-20, 22, and 24-27 are shown in Figures 29-37, respectively. Compounds were added to tubulin (1mg/ml) to a concentration of 10 μ M. The quantity of microtubules formed with epothilone A was defined as 100%.

On page 6, lines 30-32, please replace the paragraph with the following amended paragraph:

Figures 39(A) and 39(B) show epothilone A and epothilone analogues #1-7. Potencies against human leukemia CCRF-CEM (sensitive) and CCRF-CEM/VBL MDR (resistant) sublines are shown in round and square brackets, respectively.

On page 6, lines 34-36, please replace the paragraph with the following amended paragraph:

Figures 40(A) and 40(B) show epothilone B and epothilone analogues #8-16. Potencies against human leukemia CCRF-CEM (sensitive) and CCRF-CEM/VBL MDR (resistant) sublines are shown in round and square brackets, respectively.

On page 7, lines 1-3, please replace the paragraph with the following amended paragraph:

Figures 41(A) and 41(B) show epothilone analogues #17-25. Potencies against human leukemia CCRF-CEM (sensitive) and CCRF-CEM/VBL MDR (resistant) sublines are shown in round and square brackets, respectively.

On page 7, lines 5-7, please replace the paragraph with the following amended paragraph:

Figures 42(A) and 42(B) show epothilone analogues #26-34. Potencies against human leukemia CCRF-CEM (sensitive) and CCRF-CEM/VBL MDR (resistant) sublines are shown in round and square brackets, respectively.

On page 7, lines 10-12, please replace the paragraph with the following amended paragraph:

Figures 42(C) and 42(D) show epothilone analogues #35-46. Potencies against human leukemia CCRF-CEM (sensitive) and CCRF-CEM/VBL MDR (resistant) sublines are shown in round and square brackets, respectively.

On page 7, line 14, please replace the paragraph with the following amended paragraph:

Figure 42(E) shows epothilone analogues #47-49.

REMARKS

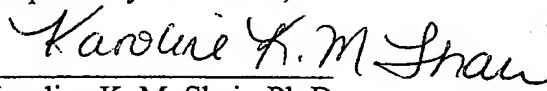
Applicants respectfully request entrance of the amendments as detailed above, in the continuation application filed herewith under 37 C.F.R. § 1.53(b). Applicants respectfully submit that no new matter is presented with these amendments. Rather, the original specification, as filed on December 3, 1997, for the parent application 08/986,025, now issued as U.S. Patent, 6,242,469 has been provided for filing under 37 C.F.R. §1.53 (b), which same specification was provided for filing of co-pending parent application number 09/874,514, filed June 5, 2001. Applicants respectfully submit that this preliminary amendment is requested to correct formal matters in the specification (e.g., addition of a statement of continuation application status (with incorporation by reference), addition of a statement regarding government support, and ensuring consistency between the specification and formal drawings). As required, Applicants have submitted herewith replacement sections and paragraphs for those sections and paragraphs that have been amended as detailed above.

Additionally, Applicants would like to bring a typographical error in the declaration to

the Examiner's attention. Specifically, the name of one inventor Dongfang Meng is incorrectly listed as Dang Fang Meng. Applicants respectfully submit that the correct spelling is Dongfang Meng. As set forth in MPEP 605.04(b), "when a typographical or transliteration error in the spelling of an inventor's name is discovered during the pendency of an application, a petition is not required, nor is a new oath or declaration under 37 CFR 1.63 needed". Applicants thus respectfully request that reference is made to this notification on the declaration so that any further correspondence (e.g., filing receipts) and issued patents will reflect the correct spelling of his name.

Applicants would like to thank the Examiner in advance for review of this request. If it is believed that a telephone conversation would expedite matters, the Examiner is invited to contact the undersigned at (617) 248-5216. The Examiner's attention is also directed to the recent change in power of attorney and correspondence address, as submitted herewith. Although it is believed that there is no fee associated with this amendment, if Applicants are mistaken, please charge any fees to our Deposit Account No.: 03-1721.

Respectfully Submitted,


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